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Dynamic hyperinflation after metronome-paced hyperventilation in COPD— A 2 year follow-up

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KEYWORDS
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Summary
In contrast to the decline in FEV_1, the behavior of dynamic hyperinflation (DH) over time is unknown in patients with COPD. Metronome-paced hyperventilation (MPH) is a simple applicable surrogate for exercise to detect DH.
Objective: To evaluate changes in MPH-induced DH during two years follow-up in mild-to-severe COPD patients. Additionally, influence of smoking status on DH and the relation between DH and other lung function parameters were assessed.
Methods: Patients were recruited from a randomized controlled trial conducted in general practice. Measurements of lung function and DH were performed at baseline and after 12 and 24 months. DH was assessed by MPH with breathing frequency set at twice the baseline rate. Change in inspiratory capacity after MPH was used to reflect change in end-expiratory lung volume and therefore DH, presuming constant total lung capacity.
Results: During follow-up, 68 patients completed all measurements. DH increased by 0.23 $\pm$0.06 L ($p \leq 0.001$). No significant changes in FEV_1 %pred were seen. Smokers had lower FEV_1 and a more rapid decline than non-smokers. DH in smokers increased more over time compared to non-smokers. The amount of DH correlated positively with resting inspiratory capacity.
Conclusion: After two years, a significant increase in MPH-induced DH in COPD patients was demonstrated, which was not accompanied by a decline in FEV_1. It might be that DH is a sensitive measure to track consequences of changes in airflow obstruction.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease with major impact on individual patients' quality of life. According to ATS/ERS consensus statements, forced expiratory volume in 1 s (FEV_1) is used worldwide to diagnose and stage COPD.[1] FEV_1 and the rate of its decline are both predictors of mortality.[2,3] However, this parameter of disease progression fails to be a reliable predictor of patient centred outcomes like exercise tolerance, dyspnoea or health related quality of life.[4] In these outcomes, changes in operating lung volumes appear to play a more important role.[5] The origin of these changes in lung volumes is dynamic hyperinflation (DH), which is defined as a transient increase in end-expiratory lung volume (EELV) as a result of increasing ventilation with concomitant expiratory flow limitation. In contrast to the decline in FEV_1 over time, reflecting the progression in disease, the behavior of dynamic lung volumes over time is unknown.

One explanation for this lack of information might be that measurements of DH during exercise are quite time consuming. DH is commonly estimated by measuring change in inspiratory capacity (IC) during exercise, which reflects change in EELV. Gelb et al. compared DH after incremental cycle ergometry and metronome-paced hyperventilation (MPH) in COPD patients.[6] IC was measured at rest and immediately after 20 s MPH with breathing frequency set at twice the resting rate.[6] The change in IC after MPH was comparable to the change in IC after incremental cycle ergometry. Therefore, MPH is a simple applicable surrogate for exercise to detect DH. This offers a practical solution to study changes in DH over time. The purpose of the present study was to evaluate changes in MPH-induced DH during two years of follow-up in patients with COPD. In addition, the influence of smoking status on DH was explored and the relation between DH and other lung function parameters was assessed.

Methods

Subjects

Patients were recruited from a randomized controlled trial comparing three different modes of COPD disease management in general practice, conducted by the Department of Primary and Community Care of the Radboud University Nijmegen Medical Centre. Details of this trial are described at http://ClinicalTrials.gov, identifier NCT00128765.

Inclusion criteria were mild-to-severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification[1] and age $\geq$35 years. Exclusion criteria were GOLD stage IV, treatment by a chest physician and severe co-morbidity with reduced life expectancy. An additional exclusion criterion for the present study was the inability to visit our pulmonary function unit. This study was approved by the local medical ethics committee. All participants gave written informed consent.

Study design

In the present study, IC measurements and spirometry were the primary outcomes. Measurements were performed at baseline and after 12 and 24 months. Patients were free of exacerbation during testing. Prescriptions for pulmonary medication during the study were extracted from the general practitioners' medical records.

Spirometry and IC measurements

Patients were instructed to continue their usual medication, but to withhold short-acting β_2-agonists and/or anti-cholinergics for 6 and 8 h respectively and long-acting β_2-agonists and/or anti-cholinergics for 12 and 24 h respectively prior to testing. Pulmonary function was measured using a spirometer (Masterlab®, Jaeger, Würzburg, Germany) according to the guidelines of the ATS/ERS.[7] IC maneuvers were performed before and immediately after 20 s MPH with breathing frequency set at twice the current resting rate.[6] Patients were instructed to take a deep breath in after normal exhalation and encouraged to inspire maximally (to the total lung capacity (TLC)). During MPH, patients were encouraged to maintain a tidal volume (VT) equal to resting VT. Performance of the test was monitored by the real-time display of breathing volumes. Any inconsistency in the last breath preceding the IC was manually corrected to obtain a true EELV.[8]

Repeatability of the IC's has been tested in a subgroup. In 18 patients, the mean coefficients of variation of resting IC (IC_{rest}) and IC after MPH (IC_{MPH}) were $2.6 \pm 1.8\%$ and $3.3 \pm 3.1\%$ respectively.

Spirometry and IC maneuvers were repeated after administration of 80 μg ipratropium/400 μg salbutamol. If not stated otherwise, post-bronchodilation values are presented in the results.

Predicted IC_{rest} was calculated as predicted TLC minus the predicted functional residual capacity. Change in IC (ΔIC: $IC_{MPH} - IC_{rest}$) was used to reflect DH, presuming constant TLC.[9,10] Inspiratory reserve volume (IRV) was calculated as IC $-$ VT. Minute ventilation was calculated by breathing frequency $\times$ VT.

Statistical analysis

Data are expressed as mean $\pm$ se. Changes in lung function parameters and DH over time were analysed with general linear models for repeated measures (two-factor mixed design: time and group). Post hoc analyses were performed with Bonferroni (time) and Scheffé (group) corrections for multiple comparisons. Differences between pre- and post-bronchodilation values were tested with a two-way repeated measures design. Pearson correlation coefficient was used to evaluate associations between lung function parameters and DH. Statistical significance was set at $p < 0.05$. Data were analysed with SPSS, version 16.0 (SPSS, Chicago, IL).

Results

Study population

After initial screening, 124 patients were included in the current study. During two years of follow-up, 68 patients completed all measurements (Fig. 1). Reasons for drop-out

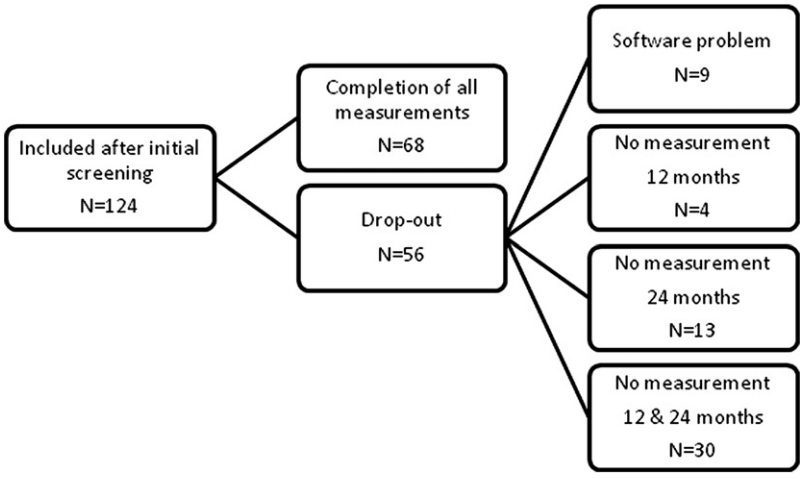

Figure 1 Overview of the number of participants initially included and those remaining after two years.

were the incapacity to visit our laboratory ($n = 15$), the occurrence of co-morbidity with reduced life expectancy ($n = 3$), death ($n = 4$), software problems ($n = 9$) or unknown ($n = 25$).

Patient characteristics

Sixty-eight patients (GOLD I $n = 8$, GOLD II $n = 47$, GOLD III $n = 13$) had complete follow-up. Seventy-two percent of the study population was male. Mean age at baseline was 64 ± 1 years and body mass index was 26.4 ± 0.5 kg/m^2.

Patients who were excluded because of missing data or withdrawal had similar baseline characteristics as those with complete data sets (data not shown). Twenty-nine percent used any long-acting bronchodilator and 16% used tiotropium. Mean post-bronchodilation FEV_1 at baseline was 66% of predicted. Mean MPH-induced ΔIC at baseline was -0.44 L.

Differences between management groups during follow-up

Patient characteristics, lung function parameters and DH were similar in the disease management groups at baseline and during two year follow-up. In addition, prescription of long-acting bronchodilation and drop-out rate were comparable between the management groups. Therefore, follow-up analyses are described without separate group values.

Course of lung function parameters and dynamic hyperinflation

Pre- and post-bronchodilation results are presented in Table 1A and B respectively. Post-bronchodilation values of FEV_1 (L and %pred), IC_{rest} (L and %pred), IRV after MPH, ventilation after MPH and change in ventilation from rest to MPH (Δventilation) were significantly greater than pre-bronchodilation values at all time points (all $p < 0.001$). The rate of DH ($\Delta IC/\Delta$ventilation) was significantly smaller after bronchodilation ($p < 0.001$).

During the two years follow-up, there was no significant decrease in post-bronchodilation FEV_1 %pred, although absolute FEV_1 slightly decreased (0.06 ± 0.02 L, 95%CI 0.00—0.12 L; $p < 0.05$) (Table 1B). IC_{rest} improved significantly during follow-up with 7 ± 2%pred (95%CI 1.9—11.7 %pred; $p < 0.01$).

Table 1A Pre-bronchodilation follow-up lung function parameters.

	Baseline	12 months	24 months
FEV_1 (L)	1.67 ± 0.06	1.63 ± 0.06	1.61 ± 0.07*
FEV_1 (%pred)	57 ± 2	56 ± 2	56 ± 2
IC_{rest} (L)	2.74 ± 0.08	2.72 ± 0.08	2.85 ± 0.09
IC_{rest} (%pred)	98 ± 2	98 ± 2	103 ± 2
ΔIC (L)	-0.51 ± 0.04	-0.61 ± 0.04	-0.62 ± 0.04
IRV_{MPH} (L)	1.31 ± 0.07	1.18 ± 0.05	1.29 ± 0.06**
Ve_{MPH} (L/min)	26.0 ± 1.1	27.5 ± 1.3	28.7 ± 1.1*
ΔVe (L/min)	13.8 ± 0.8	14.2 ± 1.1	12.7 ± 0.9
$\Delta IC/\Delta Ve$ (L/L/min)	-0.05 ± 0.01	-0.07 ± 0.01	-0.09 ± 0.02

All values are mean $\pm$ se.
Abbreviations: FEV_1: forced expiratory volume in 1 s; IC: inspiratory capacity; Δ: MPH-rest; IRV: inspiratory reserve volume; MPH: metronome-paced hyperventilation; Ve: ventilation.
*: $p < 0.05$ versus baseline; **: $p < 0.05$ versus 12 months.

Table 1B Post-bronchodilation follow-up lung function parameters.

	Baseline	12 months	24 months
FEV_1 (L)	1.92 ± 0.07	1.87 ± 0.07	1.86 ± 0.07*
FEV_1 (%pred)	66 ± 2	64 ± 2	65 ± 2
IC_{rest} (L)	2.93 ± 0.08	2.96 ± 0.09	3.09 ± 0.09*
IC_{rest} (%pred)	105 ± 2	107 ± 3	112 ± 2**
ΔIC (L)	-0.44 ± 0.04	-0.49 ± 0.04	-0.66 ± 0.05***¤
IRV_{MPH} (L)	1.53 ± 0.07	1.47 ± 0.07	1.41 ± 0.06
Ve_{MPH} (L/min)	28.6 ± 1.4	30.9 ± 1.4	32.7 ± 1.5**
ΔVe (L/min)	15.9 ± 1.1	17.2 ± 1.1	14.9 ± 1.0
ΔIC/ΔVe (L/L/min)	-0.04 ± 0.00	-0.03 ± 0.00	-0.07 ± 0.01***¤¤

All values are mean ± se.
Abbreviations: FEV_1: forced expiratory volume in 1 s; IC: inspiratory capacity; Δ: MPH-rest; IRV: inspiratory reserve volume; MPH: metronome-paced hyperventilation; Ve: ventilation.
*: $p < 0.05$ versus baseline; **: $p < 0.01$ versus baseline; ***: $p \leq 0.001$ versus baseline; ¤: $p < 0.05$ versus 12 months; ¤¤: $p < 0.01$ versus 12 months.

MPH-induced DH increased by 0.23 ± 0.06 L (95%CI 0.09—0.37 L; $p \leq 0.001$) during the 2 year follow-up period (Table 1B). VT did not change over time and breathing frequency at rest and during MPH increased slightly from baseline to 24 months (1 and 2 breaths/min respectively; $p < 0.05$). This resulted in higher minute ventilation at 24 months (Table 1B). However, change in ventilation from rest to MPH did not significantly differ between baseline and follow-up measurements. Furthermore, when ΔIC was expressed per change in ventilation, a higher rate of DH was shown during follow-up. IRV after MPH did not change significantly over time.

Sixty-three percent of the patients had at least one prescription for any long-acting bronchodilator during the study. These patients had lower FEV_1 %pred than those who did not have a long-acting bronchodilator prescription ($p < 0.05$), but the rate of decline was equal. IC_{rest} was comparable between these groups. The 40% of patients receiving at least one prescription for tiotropium, also had smaller FEV_1 %pred ($p < 0.01$) than those who were not prescribed tiotropium. FEV_1 %pred rate of decline and IC_{rest} were similar among these groups.

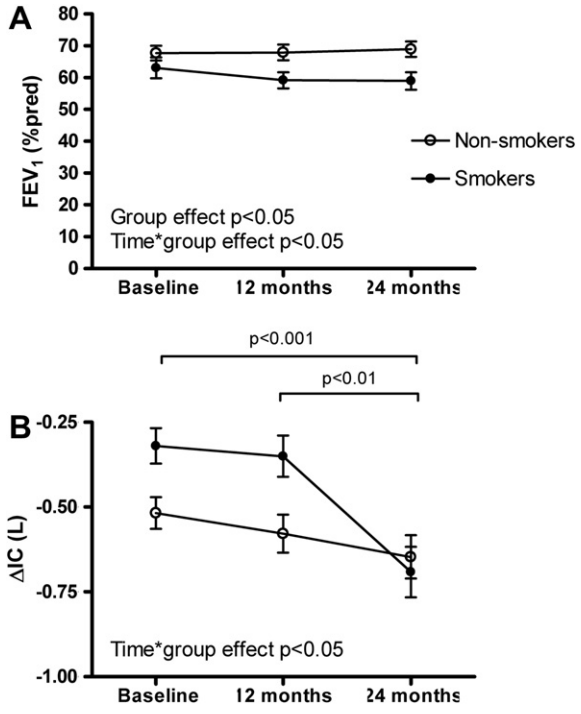

Figure 2 A: FEV_1 %pred at baseline, 12 and 24 months for smokers and non-smokers. B: ΔIC after MPH at baseline, 12 and 24 months for smokers and non-smokers.

Influence of smoking status

The group of current smokers ($n = 27$) had a different gender distribution compared to current non-smokers ($n = 41$) (56 and 83% male respectively; $p < 0.001$). Furthermore, smokers were younger than non-smokers (age 61 ± 1 and 66 ± 1 years respectively; $p < 0.05$). Therefore, only relative measures were used for comparisons between these groups. Smokers had smaller FEV_1 values and a more rapid decline (Fig. 2A). Resting IC at baseline was 99 ± 4%pred in smokers and 109 ± 3%pred in non-smokers ($p < 0.001$), but improved equally in both groups. Ventilation and change in ventilation from rest to MPH were similar in the groups. DH in smokers increased more over time (Fig. 2B). This did not result in a significant difference in IRV between the groups.

Correlations

FEV_1 correlated with IC_{rest} at baseline, 12 and 24 months ($r = 0.53$, 0.49, 0.65 respectively; all $p < 0.001$) (Fig. 3).

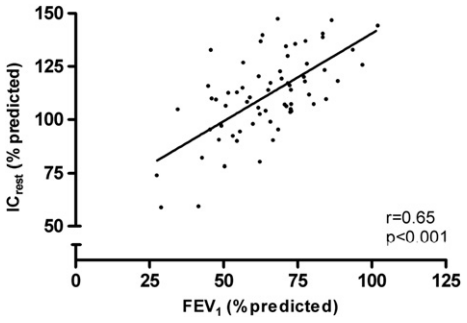

Figure 3 Correlation between FEV_1 and IC_{rest} at 24 months.

IC_{rest} (L) correlated with ΔIC ($r = -0.44$, -0.43, -0.52 respectively; all $p < 0.001$) and IRV after MPH ($r = 0.59$, 0.59, 0.65 respectively; all $p < 0.001$). Thus, larger IC_{rest} was associated with more DH, but with greater IRV after MPH. No correlation was found between FEV_1 and ΔIC. However, FEV_1 %pred did correlate with the rate of DH ($r = 0.36$, 0.42 at baseline and 12 months; $p < 0.01$ and <0.001 respectively).

In the smokers subgroup a correlation between FEV_1 % pred and ΔIC at baseline and 12 months was found ($r = 0.43$ and $r = 0.54$ respectively, both $p < 0.05$).

Discussion

This is the first study describing changes in DH over time in patients with mild-to-severe COPD. We followed 68 patients recruited from general practice for two years and found an increase in MPH-induced DH of 0.23 L. Also, ΔIC/Δventilation, the rate of DH, increased during follow-up. Subgroup analysis revealed that smokers had a more rapid increase of DH over time than non-smokers.

It was hypothesized that DH develops only when COPD becomes severe.[11] In our subjects, increase in DH over time was not accompanied by a decline in FEV_1 %pred. Furthermore, even our milder patients already showed DH, in line with recent findings of occurrence of DH in mild and moderate COPD.[12,13] Together, these findings rather contradict the hypothesis of the development of DH in the natural history of COPD, though we recognize the fact that three measurements in two years may be too short to represent natural history.

The steeper increase in DH in smokers was accompanied by a faster decline in FEV_1, suggesting that in this subgroup airflow obstruction, as reflected by FEV_1, does contribute to the level of DH. DH is a consequence of airflow limitation, which however may not be represented entirely by FEV_1. It might be that additional parameters of flow obstruction as derived by the appliance of negative expiratory pressure[14] or measures of peripheral obstruction better reflect airflow limitation. DH could be a sensitive measure to express the consequences of changes in airflow obstruction.

IC_{rest} correlated with MPH-induced DH, which is comparable to earlier findings in which resting IC correlated with DH at peak exercise.[15] This supports the idea that the amount of DH might be partially determined by resting volumes, thus, the more space the more DH. Resting IC slightly increased during follow-up, which might be due to increased long-acting bronchodilator use.[16–18] Sixty-three percent of the subjects had a long-acting bronchodilator prescribed during follow-up. Although patients stopped their long-acting β_2-agonists and/or anti-cholinergics for 12 and 24 h respectively prior to measurements, there might still be an effect on IC_{rest}.[16–18] However, no differences in IC_{rest} were found between those who did and did not receive a prescription for a long-acting bronchodilator. Since information on the actual use of these medications is lacking, this conclusion has to be interpreted with caution. We cannot exclude the possibility that the small increase in IC_{rest} occurred due to an increase in TLC.

In our study, post-bronchodilation MPH-induced DH was approximately 0.5 L at all time points. O'Donnell et al. demonstrated that exercise-induced DH of ~0.5 L was associated with a steep increase in dyspnoea intensity.[19] This 0.5 L limit for DH was obtained in severe patients with COPD with an IRV of ~0.5 L after exercise, which also has been associated with a strong increase in dyspnoea.[19] Change in IRV has been shown to be the best predictor of dyspnoea after exercise and leads to neuromechanical dissociation.[20,21] A greater tolerance of DH after bronchodilation versus placebo[19] indicates that relevant DH probably cannot be represented by a fixed amount. Probably, DH together with decreased resting IC leads to a critically small IRV and therefore to dyspnoea with consequent exercise intolerance.

In our study, IRV after MPH did not reach the critical limit of ~0.5 L.[19,20] This might be partially explained by a lower VT during MPH compared to exercise. The low VT/IC ratio after MPH (~0.4) indicates that there would have been more room to expand VT. However, Ofir et al. have shown that even with greater VT, IRV is preserved in milder patients. They studied patients with comparable resting IC, equal amounts of DH, but greater VT/IC ratios (~0.7) during peak exercise. Despite larger VT, those subjects did not reach the critical limit of IRV.[12] This supports our idea that the relatively large resting IC is the main reason that a critical IRV is not reached during MPH in our population.

There are some study limitations that need to be addressed. Our population was subject to a disease management intervention. No differences between the management groups in patient characteristics, and lung function indices and MPH-induced DH over time were seen. However, there might be an overall positive in-study effect on lung function. Furthermore, we did not assess TLC. The IC/TLC ratio at rest would have given an additional description of static hyperinflation over time. Also, ventilation increased over time, which suggests some bias in the increase in DH. However, change in ventilation from rest to MPH did not alter and the rate of DH (ΔIC/Δventilation) increased, which is consistent with the increase in DH.

Finally, drop-out was considerable, ~40%, which compromises generalizability of the results, but was comparable with other COPD trials.[22,23]

Conclusion

After a two year follow-up significant increase in MPH-induced DH in patients with mild-to-severe COPD was demonstrated, in the absence of change in FEV_1 %pred. It might be that DH is a sensitive measure to track consequences of changes in airflow obstruction.

Future studies should be directed at elucidating factors that determine DH and at investigating the clinical relevance of DH, especially in patients with mild and moderate COPD.

Conflict of interest statement

JH, AL, EB, HvH, RD and YH have no conflicts of interest to declare.

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